REMARKS

Summary of 19 February 2009 Interview

The Interview Summary mailed February 25, 2009 reflects the substance of the interview of February 19, 2009. The foregoing amendments reflect Examiners' suggestions regarding the method claims, and are presented for the purpose of advancing prosecution and without acquiescing to Examiners' rejection.

Response to Final Office Action mailed September 11, 2008

Claim 40 is pending in the application and claims 34-38 and 41-45 have been canceled. Support for amended claim 40 can be found in the specification as filed on page 5, paragraph 4; page 6, paragraph 4; page 8, paragraphs 1 and 2; and page 10, paragraphs 1 and 3.

In the September 11, 2008 Office Action, claims 34-38 and 40-45 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Krebber et al. (1997) *J. Mol. Biol.* 268:607-618 (cited in the IDS) in view of Mersmann et al. (1998) *J. of Immunological Methods* 220:51-58 and further in view of Pluckthun et al. (1996) Producing antibodies in Escherichia coli: from PCR to fermentation, Chapter 10 pages 203-252 in *Antibody Engineering* edited by John McCafferty, Hennie Hoogenboom and Dave Chiswell published by Oxford University Press. The specific grounds for rejection, and applicants' response thereto, are set forth in detail below.

Rejections Under 35 U.S.C. §103(a)

As claims 34-38 and 41-45 have been cancelled, the rejection as to those claims is moot. Regarding currently pending claim 40, the Examiner asserts that Krebber teaches a method for the expression of a polypeptide/protein comprising expressing a nucleic acid encoding a fusion protein in a host cell to form inclusion bodies, where the fusion protein comprises a first N-terminal domain of gene III protein and a polypeptide/protein. Specifically, the Examiner states that the N1, N2 and N1-N2 were expressed without signal sequence and obtained as cytoplasmic inclusion bodies. The Examiner further asserts that Krebber teaches the steps of solubilising, refolding and purifying the fusion protein.

The Examiner admits that Krebber fails to disclose nucleic acids encoding the gene III fragment linked to a sequence that is 200 to 1500 base pairs long and is derived from a eukaryotic organism. This deficiency allegedly is remedied by Mersmann, which teaches phage

display of antibody fusion proteins containing a signal sequence, where the antibody sequence falls within the length limitations specific in the instant claims and is derived from a eukaryotic organism.

Pluckthun allegedly provides insight as to what motivates one of ordinary skill in the art to practice the method of Mersmann in the method of Krebber such that gIII fusion proteins will be expressed and accumulate in the inclusion body.

Applicant respectfully traverses.

The entire focus of Krebber is directed to gene III fusions that contain a signal sequence, where the fusion protein is exported to the bacterial periplasm once produced. As the Examiner is aware, this type of construct is exactly the opposite of the present invention, as applicant's construct lacks a signal sequence. The constructs in Figure 3c, specifically cited by the Examiner in the office action, all contain a signal sequence, as described at page 609, right hand column, of Krebber ("[i]n all constructs (Figure 3c) the Bla-gIIIp fusion proteins were transported to the periplasm by signal sequences of either PelB, OmpA or gIIIp.")

The Examiner correctly notes that Krebber also describes an instance of a nucleic acid encoding an N-terminal domain of gene III attached to a short 10-amino acid histidine tag ("His-tag") having the sequence SGCPHHHHH (see, Figure 3d), for purifying the gene III protein. This construct lacks a signal sequence and is relied upon by the Examiner for a suggestion to make gene III fusions that lack a signal sequence. However, as the Examiner acknowledges, the His-tag does not meet the limitation of the instant claims of being either a genomic DNA fragment or an expressed sequence tag (EST), nor is it 100-1500 base pairs in length – rather, it is encoded by 30 base pairs of DNA. In sum, Krebber provides no motivation whatsoever to one skilled in the art to prepare *any* construct encoding a gene III fragment and a genomic DNA fragment or EST, regardless of the length of the genomic fragment or EST.

The Examiner cites Mersmann as teaching fusions with antibody fragments where those fragments are encoded by nucleic acid sequences having the length recited in the instant claims. However, the Examiner is combining apples and oranges: one of ordinary skill in the art would not have been motivated to combine the nucleic acid disclosed by Krebber, where the construct lacks a signal sequence, with the nucleic acid disclosed by Mersmann, where all the constructs contain a signal sequence. The instant claims explicitly recite that the claimed nucleic acid

molecule lacks a signal sequence for transport of the fusion protein to the bacterial periplasm. Mersmann provides no suggestion whatsoever to prepare a construct lacking a signal sequence – indeed, the opposite is true since Mersmann deals with classic display methodology where gene III fusion proteins are transported to the bacterial periplasm to combine with other phage proteins to make phage particles displaying polypeptides. Thus, one of ordinary skill in the art reading Mersmann would have been motivated to display fusion proteins *on the surface* of phage, rather than expressing the fusion protein in a manner that means that the proteins cannot reach the surface of the phage and instead accumulate *inside* the bacterial host. In this sense, Mersmann can be seen as teaching away from the instantly claimed invention by suggesting that gene III fusion proteins should contain a signal sequence and that the fusion protein should be displayed on the surface of a phage particle.

Pluckthun does nothing to cure the deficiencies of the primary references. As stated in the instant specification, the fusion proteins encoded by the claimed nucleic acids are useful for, for example, screening antibody libraries, and particularly libraries of antibodies displayed on phage, for binders that will specifically recognize the fusion partner that is fused to the first N-terminal domain of the gene III protein. Thus, the claimed method expresses (poly)peptides that can be considered to be *antigens* that can be used in screening against phage antibody libraries.

By contrast, the Examiner's comments regarding Pluckthun focus on the refolding of antibodies produced in *E. coli* and formation of "crucial" disulfide bonds in those refolded antibodies. Applicants respectfully do not understand the significance of the Examiner's reference to antibody refolding or disulfide bond formation, and further point out that nothing in Pluckthun would have motivated one of ordinary skill in the art to have prepared the instantly claimed nucleic acids. Moreover, it is notable that the recombinant antibodies described by Pluckthun are not fusion proteins where the antibody is fused with the first N-terminal domain of the gene III protein. At most, Pluckthun can be taken as suggesting that proteins produced intracellularly in inclusion bodies can be solubilized and refolded. This is not, in itself, a controversial proposition. But it fails completely to provide the missing motivation that would have been required by one of ordinary skill in the art to practice the instantly claimed method using the claimed nucleic acids. Thus, Pluckthun cannot provide any motivation to practice the

instantly claimed method using the claimed nucleic acids that encode fusion proteins when it fails to teach or suggest such fusion proteins.

In summary, Krebber deals mainly with fusion proteins that contain a signal sequence and, in the single instance where the fusion protein lacks a signal sequence, the fusion partner is merely a very short, artificial, purification tag where the gene III protein (N1, N2 or N1-N2) is the protein of interest, not a fusion protein. Mersman deals only with phage antibody display where the fusion protein contains a signal sequence and provides no suggestion whatsoever that there would be any reason to remove the signal sequence – indeed, one of ordinary skill in the art would recognize that the presence of a signal sequence is absolutely necessary to the working of the methods described by Mersman. Pluckthun deals only with the practical aspects of expressing and refolding recombinant antibodies in *E. coli* and has nothing to do with making fusion proteins encoded by nucleic acids where genomic DNA fragments or ESTs are fused to the first N-terminal domain of the gene III protein.

The only suggestion to fuse genomic DNA fragments or ESTs to nucleic acid encoding the first N-terminal domain of the gene III protein of filamentous phage is found in the specification of the instant application. Even if the Examiner were correct that Mersmann, Krebber and Pluckthun somehow can be combined, the absence of any rationale for making the combination makes the instant rejection flawed. Accordingly, withdrawal of the rejection respectfully is requested.

As background, a major challenge of using phage display methods to screen libaries of binding molecules, such as antibodies, is to minimize non-specific adsorption of the phages in the binding procedure and, by so doing, increase the number of specific binders. This is particularly the case where (a) the selected target is uncharacterized or only poorly characterized, which is often the case with (poly)peptides encoded by an EST or by a genomic fragment, and (b) when *fusion* proteins have to be used, because fusion proteins always contain, besides the desired target protein, at least one further unwanted part which will also serve as a potential target for some of the members of the binder library.

The present inventors have recognized that a recombinant library of antibodies displayed on the surface of a filamentous phage automatically removes individual phages which display Nl-binding immunoglobulins on their surface- in other words, no binders are found that bind to

N1. This is presumably because the filamentous phage carry gene III on their surface which serves as a target for any N1-binding antibody, leaving them unavailable for binding elsewhere and eliminating those phage from the library. The Nl-containing fusion protein encoded by the instantly claimed nucleic acids is, therefore, surprisingly and unexpectedly effective for identifying specific binders for an unknown and/or uncharacterized (poly)peptide encoded by an EST or by a genomic fragment. See, for example, Example 1 on page 19 of the instant specification, which clearly demonstrates that a filamentous phage library surprisingly does not contain *any* Nl-binder (*"[i]n pannings Na and Nb, no binders against Nl were obtained...* ").

Prior to the recognition of this important effect by the present inventors there was no motivation in the art to practice the instantly method using the claimed nucleic acids which encode the first N-terminal domain of the gene III protein of filamentous phage fused to a (poly)peptide encoded by a genomic DNA fragment or an EST from a eukaryotic cell. In the absence of any such motivation, no *prima facie* case of obviousness exists, and withdrawal of the rejection respectfully is requested.

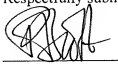
Finally, it is axiomatic that it is improper to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art. In the instant case, the combination of Krebber and Mersmann is improper because it ignores the key distinction that the fusion proteins described by Mersmann all contain a signal sequence. For at least these reasons, there would have been no motivation for one of ordinary skill in the art to combine Mersmann with Krebber and the rejection is improper and should be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, applicants respectfully submit that the application is in condition for allowance. Should the Examiner feel that there are any issues outstanding after consideration of this response, the Examiner is invited to contact the undersigned to expedite prosecution of the application.

The Commissioner is hereby authorized by this paper to charge any fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-3840. **This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. § 1.136(a)(3).**

Respectfully submitted,



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